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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/665,852	09/20/2000	Guangping Gao	GNVPN.030AUSA	6419

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	4

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/665,852	Applicant(s) GAO ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,258,595 in view of Fields et al. (Virology. Vol. 2., 3rd edition. 1995. Philadelphia: Lippencott Willims and Wilkins; page 2183).

The instant claims are drawn to a host cell comprising a transgene, rep/cap, E1a, E1b, and E2a, which are all under individually controlled regulatory sequences. E1a, E1b, and E2a are expressed under various promoters. The patent claims are drawn to methods for producing AAV by culturing host cells with rep and cap sequences (see especially claims 1 and 3) and additionally supplying the cells with an adenovirus/AAV (Ad/AAV) hybrid virus that has E1a and E1b under the control of different promoters (see especially claims 14-19). The patent does not claim E2a under the control of an inducible promoter. However, Fields et al. teaches that E2a encodes products necessary for DNA-binding protein necessary for adenovirus DNA synthesis as well as stimulating

AAV transcription and regulating transcripts from the nucleus to the cytoplasm, see the first full paragraph of the second column on page 2183. One of ordinary skill in the art at the time the invention was made would have been motivated to express of E2a from a recombinant promoter in an Ad/AAV hybrid to control synthesis of obligatory Ad genes required for AAV replication (see the first paragraph of Fields et al. under "helper functions") and the amount of AAV gene transcripts being processed into the cytoplasm. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because there are a number of conventional inducible promoters that would readily control the expression of the E2a gene product. Therefore, the claims in the instant application would have been prima facie obvious to the ordinary artisan in view of '595 and Fields et al., absent unexpected results.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 9, 11, 14, 15, 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson et al. (5,856,152).

The claims are drawn to a cell comprising a transgene flanked by AAV ITRs expressed by a promoter, rep/cap, and DNA expressing E1a and E2a gene products, which are integrated in to the host chromosome, present as an episome, or transiently expressed. The transgene is supplied by a rAAV. The rAAV produced is in the absence

of a helper virus and is purified from the culture and free of wild type and helper adenovirus.

Wilson et al. teaches a host cell comprising a transgene flanked by ITRs, rep/cap, E1a and E2a gene products integrated into the host cell chromosome. The transgene is supplied by rAAV, stably integrated into the host chromosome, and is produced in the absence of helper virus. In addition, Wilson et al. teaches purification of the recombinant virus particles from cellular lysate. See claims 1-8, column 8, lines 49-56, column 10, lines 44-47, column 11, line 65-column 12, line 14, and column 13, lines 7-15 and column 22, line 29- column 24, line 28.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. as applied to claims 1, 2, 9, 11, 14, 15, 21-24 above, and further in view of Alkhatib et al. (Journal of Virology. 1988; 62 (8): 2718-27, abstract only) and Fields et al. as set forth *supra*.

The claims are drawn to expressing E2a and the transgene on the same vector (cl.10), expressing E1a and E1b on the same vector (cl.12), and replacing E1a and E1b with the transgene and expressing E1a and E1b in place of E3 (cl.13).

See the teachings of Wilson et al. above. Wilson et al. does not teach any of the vectors or replacements recited above.

However, Alkhatib et al. teaches that a MV HA coding region that replaced the E1a and E1b region in Ad 5 genome resulted in high titers of stable viruses recombinant viruses in 293 cells supplying E1a and E1b functions.

One of ordinary skill in the art at the time the invention was made would have been motivated to replace E1a and E1b with a transgene to obtain high titers of stable virus in the method of producing recombinant AAV viruses with hybrid Ad/AAV vectors taught by Wilson et al. One of ordinary skill would have had a reasonable expectation in producing the claimed invention because Wilson et al. teaches that E1 and E3 regions can be deleted and replaced with heterologous AAV sequences, see column 6, lines 45-60 and column 8, lines 6-12.

Alkhatib et al. also teaches that the recombinant viral titers were obtained from 293 cells (helper cells) which supply E1a-E2b functions. Wilson et al. teaches that helper viruses are optional, see claim 1. One of ordinary skill in the art at the time the invention was made would have been motivated to express E1a and E1b in a separate vector in order to supply the necessary elements required for AAV and Ad gene expression, such as those taught by Fields et al. to produce recombinant viruses in a cell line other than 293. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Alkhatib et al. teaches that replacing E1a-E1b is useful for producing hybrid adenoviruses and Wilson et al. uses hybrid adenovirus/AAV viruses for transgene expression in cells.

Fields et al. teaches that E2a is necessary for DNA-binding protein necessary for adenovirus DNA synthesis as well as stimulating AAV transcription and regulating transcripts from the nucleus to the cytoplasm, see the first full paragraph of the second

column on page 2183. One of ordinary skill in the art would have been motivated to express E2a with the transgene on the same vector in order to ensure transport of the transgene of Wilson et al. to the cytoplasm and stimulate transcription of the transgene between AAV ITRs. The ordinary artisan would have had a reasonable expectation in producing the claimed invention because Wilson et al. also teaches E2a is required for expression of adenovirus genes, see column 10, lines 37-39.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 3-8 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., Alkhatib et al., and Fields et al. as applied to claims 1, 2, 9, 10-15, 21-24 above.

The claims are drawn to directing the expression of E1a, E1b, and E2a from various promoters.

None of the references teach expressing the various gene products with various inducible promoters. However, it is well known in the prior art that excessive accumulation of E1 and E2a gene products are toxic to cells. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to express each of the products from different promoters to control the amount of expression of each gene and eliminate the amount of toxicity to the cells and express as much recombinant virus as the cells are able to produce. Limitations drawn to specific types of promoters are obvious modifications related to establishing normal reaction conditions and such parameters in this art would be determined by routine experimentation. Therefore, the

invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
November 17, 2001

James C. Housel 11/19/01
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